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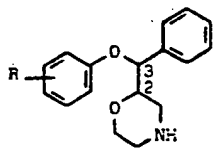
(54) Enantiomers of phenoxy derivatives of benzyl morpholine and salts thereof

(57) A 2R, 3R or 2S,3S enantiomer of a 2-(α-phenoxybenzyl)-morpholine derivative of formula (I):



(I)

wherein
R is a C_1–C_6 alkoxy group or a trihalomethyl group; and the pharmaceutically acceptable salts thereof are useful as an anti-depressant, in treating sleep disorders or as a minor tranquilizer.

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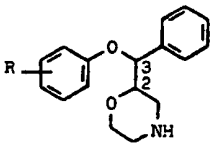
SPECIFICATION

Enantiomers of phenoxy derivatives of benzyl morpholine and salts thereof

The present invention relates to RR and SS enantiomers of phenoxy derivatives of benzyl morpholine and salts thereof, to a process for their preparation and to pharmaceutical compositions containing them. U.S. Patent No. 4,229,449 describes, among the others, 2-(α-phenoxy-benzyl)-morpholine derivatives of the following formula (I)



(I)

wherein R is a C_1-C_6 alkoxy group or a trihalomethyl group, and their pharmaceutically acceptable salts. Due to the presence of the two chiral centres at the carbon atoms 2 and 3 in the above formula (I), for each compound of formula (I) two couples of enantiomers exist. These two couples, which are in a diastereoisomeric relationship one to the other, are identified by the symbols (±) RS,RS and, respectively (±) RS,SR, in accordance with I UPAC, NOMENCLATURE OF ORGANIC CHEMISTRY, 1979 Edition, Section E, 489.

In the formula (I) and in the other formulae of this specification the two chiral centres have been conventionally numbered 2 and 3 in order to be able to indicate unequivocally the absolute configuration of each center, when available. Such a conventional numbering, however, is independent of the numbering required, e.g. by the IUPAC Nomenclature, for a correct naming of the involved compounds.

While mention of specific diastereoisomers, i.e. couples of enantiomers, of the above formula (I) was given in U.S. Patent No. 4,229,449, no specific mention was therein made of the single enantiomers deriving therefrom.

The present invention provides a 2R, 3R or 2S, 3S enantiomer of a compound of formula (I) and the pharmaceutically acceptable salts thereof. An enantiomer of the invention will therefore be either a dextro (+) or a levo (−) enantiomer. Preferred compounds of the invention are those wherein R is methoxy, ethoxy or trifluoromethyl.

The present invention includes also the metabolites, the bioprecursors and, as already said, the pharmaceutically acceptable salts of the 2R, 3R or 2S, 3S enantiomers of formula (I), as well as the pharmaceutical compositions containing the said enantiomers or their salts. Examples of pharmaceutically acceptable salts of the enantiomers of the invention are both the salts with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulphuric acid, and the salts with organic acids including optically active acids, for example, citric acid, tartaric acid, methanesulphonic acid, fumaric acid, maleic acid and mandelic acid. Preferred salts are those with hydrochloric acid and methanesulphonic acid, the more preferred ones being those with methanesulphonic acid. Examples of specific preferred compounds of the invention are the following (+) and (−) enantiomers:

(+)2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine;
(−)2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine;
(+)2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine;
(−)2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine;
(+)2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine;
(−)2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine,

and their pharmaceutically acceptable salts, in particular the salts with hydrochloric acid or methanesulphonic acid.

The compounds of the invention may be prepared by a process comprising:

(a) reacting the (±)RS,RS racemic form of a compound of formula (I), as free base, with an optically active acid, so obtaining a mixture of two diastereoisomeric salts;
(b) separating the obtained salts by crystallization;
(c) optionally liberating the dextro (+) or levo (−) enantiomeric base from the respective separated salt; and
(d) optionally salifying the obtained dextro (+) or levo (−) enantiomeric base with a pharmaceutically acceptable salt.

The reaction of the (±)RS,RS racemic form of a compound for formula (I) as free base with an optionally active acid may be carried out with any suitable optionally active acid which may be, for instance, L (+) mandelic acid, D (−) mandelic acid, 10 (+) camphorsulfonic acid, L (+) dibenzoyltartartic acid, L (−) pyrrolidon-carboxylic acid, L(+) tartaric acid or D (−) tartaric acid. This salification reaction is preferably performed in an organic, preferably anhydrous, solvent,

which may be for instance, methanol, ethanol, dioxane or dimethylformamide.

If necessary, the precipitation of the obtained salt from the reaction solvent may be favoured by adding an anhydrous apolar solvent which may be, for example, diethylether, n-hexane or cyclohexane.

The separation of the desired salt from the diastereoisomeric mixture is preferably carried out by fractional crystallization from an appropriate solvent which may be, for example, methanol or ethanol. Preferably an anhydrous solvent is used.

The optional liberation of the corresponding dextro (+) or levo (−) enantiomeric base from the separated salt may be carried out by treatment with a small excess of any suitable base. An inorganic base such as, for instance, an alkali metal or alkaline-earth metal hydroxide or carbonate or bicarbonate, is preferably used. Sodium or potassium carbonate or bicarbonate are particularly preferred bases.

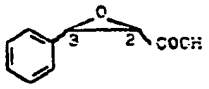
The optional salification of an obtained dextro (+) or levo (−) enantiomeric base may be carried out by reaction with a stoichiometric amount or a small excess of the desired acid in an appropriate solvent. Thus, for example, the salt with hydrochloric acid may be obtained by treatment with anhydrous gaseous hydrochloric acid or an anhydrous alcoholic solution of hydrochloric acid in an anhydrous solvent such as, e.g., diethylether, toluene, ethanol, and isolating the hydrochloride by filtration or evaporation of the solvent. Analogously, the salt with methanesulphonic acid may be obtained, for example, by adding an ethanolic solution of methanesulphonic acid to the ethanolic mixture of the enantiomeric base.

The precipitation of the methanesulphonate salt may be, if necessary, favoured by the addition of an anhydrous apolar solvent which may be for example, diethylether, n-hexane or cyclohexane.

All the reaction steps reported above from a) to d) may be carried out at a temperature varying from about 0°C to about 50°C, the room temperature being, in any case, the preferred one.

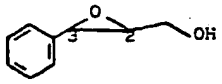
The preparation of the compounds of formula (I) as a mixture of diastereoisomers and as separated diastereoisomers is reported in U.S. patent No. 4,229,449. In an alternative approach, the compounds of the invention may be prepared by a process comprising:

(a) reducing the (+) or (−) enantiomer of a glycidic acid of formula (II)



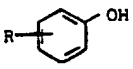
(II)

or a derivative thereof, so obtaining the (+) or (−) enantiomer of the cinnamyl alcohol-2,3-epoxide of formula (III)



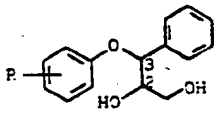
(III)

(b) reacting a (+) or (−) enantiomer of formula (III) with a phenol derivative of formula (IV)



(IV)

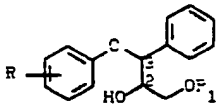
wherein R is as defined above, so obtaining a (+) or (−) enantiomer of formula (V)



(V)

wherein R is as defined above;

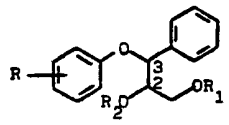
(c) esterifying a (+) or (−) enantiomer of formula (V) with a carboxylic acid, or a reactive derivative thereof, so obtaining a (+) or (−) enantiomer of formula (VI)



(VI)

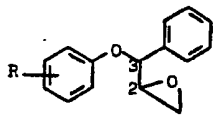
wherein R is as defined above and R_1 is the residue of a carboxylic acid;

(d) esterifying a (+) or (−) enantiomer of formula (VI) with a sulphonic acid, or a reactive derivative thereof, so obtaining a (+) or (−) enantiomer of formula (VII)



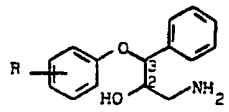
(VII)

wherein R and R_1 are as defined above and R_2 is the residue of a sulphonic acid;
(e) making an epoxide from a (+) or (−) enantiomer of formula (VII) so obtaining a (+) or (−) enantiomer of formula (VIII)



(VIII)

wherein R is as defined above;
(f) reacting a (+) or (−) enantiomer of formula (VIII) with ammonia, so obtaining a (+) or (−) enantiomer of formula (IX)

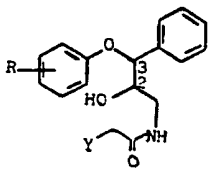


(IX)

wherein R is as defined above;
(g) reacting a (+) or (−) enantiomer of formula (IX) with a compound of formula (X)

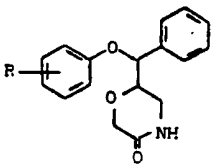
$Y-CH_2-CO-Y$ (X)

wherein Y is halogen, so obtaining a (+) or (−) enantiomer of formula (XI)



(XI)

wherein R and Y are as defined above;
(h) cyclizing a (+) or (−) enantiomer of formula (XI) so obtaining a (+) or (−) enantiomer of formula (XII)



(XII)

wherein R is as defined above; and
(i) reducing a (+) or (−) enantiomer of formula (XII) so obtaining a (+) or (−) enantiomer of formula (I) and, if desired, converting the obtained 2R,3R or 2S,3S enantiomer of formula (I) into a pharmaceutically acceptable salt thereof.

A derivative of the glycidic acid of formula (II) may be, e.g., an anhydride, preferably a mixed anhydride. The carboxylic acid employed in the above esterification step (c) may be either aliphatic, e.g. a C_2-C_6 aliphatic carboxylic acid such as, for instance, acetic or propionic acid, or aromatic, e.g. benzoic or *p*-nitro-benzoic acid.

The R_1 residue of a carboxylic acid in the above formulae (VI) and (VII) is, e.g., acetyl, propionyl, benzoyl or p-nitro-benzoyl.

The sulphonic acid employed in the esterification step (d) is, for example, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or *p*-toluenesulphonic acid. The R_2 residue of a sulphonic acid in the above formula (VII) is, e.g., methanesulphonyl, ethanesulphonyl, benzenesul-

phonyl or *p*-toluenesulphonyl, preferably methanesulphonyl. The halogen Y in the compounds of formula (X) and formula (XI) is, preferably, chlorine, bromine or iodine, most preferably chlorine.

The reduction step (a) may be carried out with BH_3 or a mixed hydride such as, e.g., $NaBH_4$ followed known procedures, preferably operating under cooling, e.g. around 0°C, in a suitable anhydrous inert solvent which may be, for instance, absolute ethanol, diethyl ether or tetrahydrofuran.

The reaction of an enantiomer of formula (III) with a compound of formula (IV) is preferably carried out by heating, e.g. at a temperature between about 60°C and about 120°C, in the presence of a base such as, e.g., aqueous sodium or potassium hydroxide, preferably in absence of any other solvent.

The esterification of an enantiomer of formula (V) to give a compound of formula (VI) is preferably performed with a reactive derivative of a carboxylic acid, preferably a carboxylic acid halide, in particular chloride, operating under cooling, e.g. at about −10°C to 0°C, or at room temperature, in an anhydrous organic solvent, e.g. benzene or toluene, in the presence of a base which may be, for example, an organic base such as, e.g., triethylamine or pyridine: according to a preferred procedure, pyridine is used as solvent in absence of any other base.

The esterification of an enantiomer of formula (VI) to give a compound of formula (VII) is preferably carried out with a reactive derivative of a sulfonic acid, preferably a sulfonic acid halide, in particular the chloride, e.g. methanesulfonyl chloride or *p*-toluenesulfonyl chloride, in the presence of an acid acceptor which may be, for instance, an organic base as triethylamine or pyridine.

The reaction is preferably performed under cooling, e.g. at −10° to 5°C, in a suitable anhydrous solvent such as, e.g., benzene, toluene, methylene chloride or pyridine: when pyridine is used as solvent, it also acts as a base. The transformation of a compound of formula (VII) into a compound of formula (VIII), is carried out by reaction with a suitable base, preferably an inorganic base such as, e.g., an alkali metal or alkaline-earth metal hydroxide, preferably sodium or potassium hydroxide. Preferably the reaction is carried out at room temperature in an aqueous organic solvent such as, e.g. dioxane or dimethylformamide.

The subsequent reaction of the epoxide of formula (VIII) with ammonia is preferably carried out at room temperature with 30–32% aqueous ammonia in a suitable solvent which may be, for instance, dimethylacetamide or an aliphatic alcohol, e.g. methanol or ethanol. The reaction between an obtained enantiomer of formula (IX) and a compound of formula (X) may be, e.g., performed in the presence of a base, e.g. an organic base such as, for instance, triethylamine, preferably operating under cooling, for example at −10°C to 0°C, in an anhydrous inert solvent, e.g. an halogenated hydrocarbon such as, e.g., methylene chloride.

The subsequent cyclization of an enantiomer of formula (XI) may be, e.g., performed by treatment with a base, for example with potassium tert.butoxide in tert.butyl alcohol at room temperature, according to known procedures.

The reduction of an obtained enantiomer of formula (XII) may be, e.g., carried out by treatment with BH_3 or a mixed hydride, for instance $LiAlH_4$ or $NaBH_4$, in an anhydrous inert solvent such as, e.g., diethylether, tetrahydrofurane, dioxane or toluene, at temperatures varying from about 0°C to the reflux temperature; a particularly suitable reduction procedure involves the use of Red-Al (Vitride ®) as the reducing agent in anhydrous toluene at room temperature.

The optional salification of an obtained enantiomer of formula (I) may be carried out in any conventional way according to known salification procedures.

The glycidic acid enantiomers of formula (II), used as starting material in the alternative process approach described above, are either known compounds or compounds that can be prepared by known methods from known compounds: see, for instance, K. Harada, J. Org. Chem., *31*, 1407, 1966.

The compounds of the invention are active on the central nervous system, in particular as antidepressant agents, as is shown, e.g., by their ability in raising the concentration of physiologically active monoamines, e.g. by blocking their uptake and/or be desensitizing α-2 presynaptic receptors. As is known, an important property of antidepressant agents is their ability of blocking neurotransmitter uptake at cerebral synapses (Iversen L.L., J.Pharm. Pharmacol., *17*:42, 1965), and further important property may also be the ability of blocking or desensitizing α-2 adrenoceptors (Chapleo C.B., J. Med. Chem. *26*:823, 1983).

The compounds of the invention were found to be able to increase the concentration of biogenic amines both *in vitro* (where activity was determined, e.g., with radioactively labelled compounds according to the experimental method described by Snyder S.H. in J. Pharmacol. Exp. Ther., 165:76, 1969) and *in vivo*, by a variety of methods.

The physiologically active monoamines whose concentration is raised by the compounds of this invention include serotonin, norepinephrine and dopamine. The antidepressant activity of the compounds of this invention is proved also be the fact that they are active in preventing reserpine-induced blepharospasm and hypotermia in mice.

The compounds of this invention may also find use, e.g., in treating disorders of sleep and as

minor tranquilizers.

The toxicity of the compounds of the invention is negligible, therefore they can be safely used in therapy.

The compounds of the present invention are preferably administered orally, although they can be administered also in other conventional ways, for example, by injection or by rectal way.

The dosage suitable for the oral administration to adult humans of the compounds of the invention, is preferably 0.5–10 mg pro dose 2–4 times a day. Pharmaceutical compositions according to the invention comprise a 2R,3R or 2S,3S enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient and a pharmaceutically acceptable carrier and/or diluent. The compositions may be prepared according to conventional methods with the usual ingredients. Thus, for oral administration, the pharmaceutical compositions containing the compounds of the invention are preferably tablets, pills or capsules which contain the active substance together with diluents, such as, for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubrificants, for instance, silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; or they may also contain binders, such as, for example, starches, gelatine, methylcellulose, gum arabic, tragacanth, polyvinylpyrrolidone; disintegrating agents, such as, for instance, starches, alginic acid, aliginates; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as, for instance, lecithin, polysorbates, laurylsulphates; and in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

Also the other pharmaceutical formulations containing the compounds of the invention may be prepared by known methods and they can be, for example, syrups or drops for the oral administration, sterile solutions for injection, or suppositories.

The following examples illustrate but do not in any way limit the present invention. Where unspecified, the $[\alpha]_D$ values are for 1% concentrations in 95% ethanol.

Example 1

To a solution of 2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine (±) RS,RS diastereoisomer (1.6 g) in anhydrous ethanol, methanesulphonic acid (0.33 ml) was added. By dilution with diethyl ether (200 ml) of a solid precipitated. This was collected by filtration to give 2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate m.p. 146–147°C, U.V. (MeOH): λ_{max}=275 nm; $E^{1\%}_{1cm}$=50, as the (±)RS,RS racemic form.

Example 2

An aqueous solution of (±) RS,RS 2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate (m.p. 146–147°C; 40 g), made basic with potassium carbonate, was extracted twice with ethyl acetate. The organic solution was washed with water, dried on sodium sulphate and evaporated to dryness *under vacuo*. The free base (31 g) was dissolved in anhydrous ethanol (140 ml) and to the solution L(+) mandelic acid (15.06 g) dissolved in anhydrous ethanol (140 ml) was added. The precipitate was filtered to give 18.85 g of a solid having m.p. 134–151°C and $[\alpha]_D^{20}$=(+) 48.01 (1% solution in 80% ethanol). After crystallization from anhydrous ethanol (200 ml), 16.86 g of a product (mandelate salt), melting at 151–153°C, were obtained; $[\alpha]_D^{20}$= +49.09 (1% solution in 80% ethanol). This mandelate salt was dissolved in H_2O, the solution was basified with potassium carbonate and the base extracted with ethyl acetate. The organic solution was dried over sodium sulphate and evaporated to dryness *under vacuo*. The oily residue consisting of (+) 2S,3S-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine (12.15 g) was taken up with ethanol and an ethanolic solution of methanesulphonic acid (3.72 g) was added. After dilution with diethyl ether a precipitate formed which was filtered to give (+) 2S,3S-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate (13.05 g); m.p. 100–102°C, $[\alpha]_D^{20}$= +21.89° (1% solution in 95% ethanol).

Molar purity (D.S.C.)=98%.

N.M.R. ($CDCl_3$)δ: 1.42 (t, 3H, CH_3–CH_2),
2.71 (s, 3H, CH_3SO_3),
2.84–3.50 (m, 4H, CH_2–N–CH_2),
3.85–4.40 (m, 3H, CH_2–O–CH),
4.05 (q, 2H, CH_2–O–Ar),
5.14 (d, 1H, O–CH–Ar),
6.64–6.92 (m, 4H, $Ar<^{o}_{o}$),
7.33 (m, 5H, Ar–CH),
9.20 (bs, 2H, $N^{+}H_2$).

The same method was used to prepare, starting from D(−) mandelic acid, the levo isomers (−) 2R,3R-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine and (−) 2R,3R-2-[α-(2-ethoxy-phenoxy)-

benzyl]-morpholine methanesulphonate, the latter having m.p. 100–102°C, $[\alpha]_D^{20} = -21.89°$ (1% solution in 95% ethanol).

By proceeding analogously, the followuing enantiomers were prepared starting from the corresponding (±) RS,RS racemic forms:

(+) 2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine;
(−) 2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine;
(+) 2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine;
(−) 2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine;
(+) 2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine methane-sulphonate;
(−) 2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine methane-sulphonate;
(+) 2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine methanesulphonate;
(−) 2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine methanesulphonate.

The optical purity of the (+) 2S,3S- and (−) 2R,3R-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonates obtained from the (±) RS,RS racemic form was determined as reported below.

To a solution of (+) 2S,3S-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine base (1 g) (obtained from the corresponding (±) RS,RS diastereoisomer) and Et_3N (0.90 ml) in anhydrous toluene (40 ml), L(−) menthoxy-acetyl-chloride (0.80 ml) in anhydrous toluene (10 ml) was added dropwise under vigorous stirring at 10°C temperature. After stirring 1 hour at room temperature, the reaction was complete and the reaction mixture was washed with water, dried over sodium sulphate and evaporated to dryness *under vacuo*.

The same procedure was applied to the (−)2R,3R-enantiomer obtained from (±) RS,RS 2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine.

Each of the two diastereoisomeric amides so obtained was analysed by HPLC technique/Partisil * PXS 10/25; cyclohexane:ethylacetate 93:7 with 0.15% of isopropylamine] to give a Retention Time (R.T.) of 15,13 min. and, respectively, of 17,23 min.

The result was in both cases a relative purity≥98.5% from which an optical purity ≥97% for both the (+) and (−) enantiomers may be inferred.

Example 3

A solution of 3.8 g (13.3 mmole) of (+) 2S,3R-phenyl-glycidic acid D(+)-α-methyl-phenethylamine salt was treated with 6.65 ml (13.3 mmole) of 2N HCl. The organic acid was extracted with diethylether and the solvent removed *in vacuo* after drying over Na_2SO_4. The residue was dissolved in 70 ml of CH_2Cl_2 and 2 ml (14.3 mmole) of triethylamine were added. The solution was cooled to 0°C and 1.36 ml (14.3 mmole) of ethyl-chlorocarbonate were added dropwise under stirring during 1 hr. After 2hr the solution was slowly added under stirring to a suspension of 2.26 g (59.7 mmole) of sodium borohydride in 17 ml of absolute ethanol, at 0°C. After 0.5 hr the temperature was allowed to rise to room temperature and stirring was continued overnight.

The mixture was poured into water and the product extracted with CH_2Cl_2. After separation on a flash chromatography column ($CHCl_3$:CH_3OH 100:2 as eluant) 0.62 g (31%) of (+) 2R,3R-cinnamyl alcohol-2,3-epoxide were obtained as a colorless oil; $[\alpha]_D^{20} = +45.9°$ (C 1.5, abs.ethanol). (Found: C, 71.68; H, 6.71. $C_9H_{10}O_2$ requires C, 71.97; H, 6.71%);

^{1}H–N.M.R. ($CDCl_3$)Δ: 3.24 (1H, ddd, –C*H*–CH_2OH),
3.76 (1H, dd, CH_AH_B–OH),
3.94 (1H, d, Ph–C*H*, J=2.1 Hz),
4.05 (1H, dd, CH_AH_B–OH),
7.35 (5H, s, Ph);

IR ($CHCl_3$) cm^{-1}: 3590–3450 (OH), 1600, 1490 (arom.C=C), 1220, 1060 (Alk-O-Alk, Alk-OH); 0.33 g (15.3%) of the starting (+)–(2S,3R) phenyl glycidic acid were recovered together with 0.92 g (36.5%) of its ethyl ester.

Example 4

To a solution of 1.77 g (44.3 mmole) of NaOH in 100 ml of water, 18.4 g (133 mmole) of 2-ethoxy-phenol were added. The mixture was stirred at 70° under nitrogen until the solid completely dissolved, and then 6.7 g (44.3 mmole) of (+) 2R,3R-cinnamyl alcohol-2,3-epoxide were added in 10 min. The solution was stirred at 70°C for 2.5 hr and then poured into 200 ml of 1N NaOH at 10–15°. After extraction with CH_2Cl_2 the organic solution was washed successively with 1N NaOH and brine. Elimination of the solvent gave 10.2 g of (+) 2R,3S-3-(2-ethoxy-phenoxy) 1,2-dihydroxy-3-phenylpropane, $[\alpha]_D^{20} = +7.8°$; m.p. 87–89°; IR (KBr) cm^{-1}: 3440–3380 (OH), 1590, 1490 (arom.C=C), 1240 (Ar-O-Alk).

Example 5

To a solution of 10 g (34.6 mmole) of (+) 2R,3S-3-(2-ethoxy-phenoxy)-1,2-dihydroxy-3-phenylpropane in 100 ml of pyridine, 6.44 g (34.0 mmole) of 4-nitro-benzoyl-chloride in 100 ml

of pyridine were added at −10° in 1.5 hr. After 0.5 hr the solution was poured into a mixture of 2 l of 2N HCl and 1300 g of ice and the oily precipitate was extracted with ethyl acetate. After an usual work-up the compound (+) 2R,3S-3-(2-ethoxy-phenoxy)-2-hydroxy-1-(4-nitro-benzoyloxy)-3-phenylpropane (8.2 g) was obtained as oil, $[\alpha]_D^{20} = +11.7°$.

Example 6

To a solution of 80 g (18.2 mmole) of (+) 2R,3S-3-(2-ethoxy-phenoxy)-2-hydroxy-1-(4-nitro-benzoyloxy)-3-phenylpropane and 3.86 ml (27.4 mmole) of triethylamine in 90 ml of CH_2Cl_2, 1.54 ml (20.0 mmole) of CH_3SO_2Cl were added dropwise at 0–5° and the solution was kept for 0.5 hr at that temperature. After washing with 10% HCl and 5% $NaHCO_3$ solutions and water, the solution was dried over Na_2SO_4 and the solvent evaporated to dryness.

After usual work-up the compound (+) 2R,3S-3-(2-ethoxyphenoxy)-2-mesyloxy-1-(4-nitroben-zoyloxy)-3-phenylpropane (7.5 g) was obtained as oil, $[\alpha]_D^{20} = +33.6°$.

Example 7

A solution of 3.95 g (7.7 mmole) of (+) 2R,3S-3-(2-ethoxyphenoxy)-2-mesyloxy-1-(4-nitroben-zoyloxy)-3-phenylpropane in 40 ml of dioxane and 16 ml of 2N NaOH was stirred for 4 hr at room temperature. After diluting with 200 ml of water the solution was extracted with ethyl acetate and the organic phase washed with a 5% aqueous solution of $NaHCO_3$ then water. After evaporation of the solvent *in vacuo* the residual oily epoxide (−) 2S,3S-3-(2-ethoxy-phenoxy)-3-phenylpropane 1,2-epoxide weighed g. 2.05 (100%) and was used as such for the subsequent step, $[\alpha]_D^{20} = -3.1°$.

Example 8

A solution of 2.05 g (7.6 mmole) of (−) 2S,3S-3-(2-ethoxyphenoxy)-3-phenylpropane 1,2-epoxide in 50 ml of methanol and 30 ml of 32% NH_4OH was kept standing in a sealed flask for 6 hr. After evaporation of the solvent the residue was dissolved in ethyl acetate, and 0.52 ml (8 mmole) of CH_3SO_3H in 10 ml of ethyl acetate were added to the solution. After 16 hr 2.13 g of a crystalline product (+) 2S,3S-1-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane was collected, m.p. 97–99°C, $[\alpha]_D^{20} = +34.4$.

Example 9

To a solution of 2.13 g (7.4 mmole) of the aminoalcohol (+) 2S,3S-1-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane and 2.27 ml (16.2 mmole) of triethylamine in 70 ml of CH_2Cl_2 kept at −5 −10°, 0.64 ml (8.0 mmole) of chloroacetylchloride dissolved in 20 ml of CH_2Cl_2 were added dropwise. After 0.5 hr the solution was washed with water, dried over $NaSO_4$ and evaporated to dryness. After usual work-up a residue of (+) 2S,3S-1-chloroacetylam-ino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane (2.6 g) was obtained as oil, $[\alpha]_D^{20} = +18.6°$.

Example 10

To a solution of 2.0 g (18.0 mmole) of potassium t-butoxide in 15 ml of tert-butanol 3.3 g (9.0 mmole) of (+) 2S,3S-1-chloroacetylamino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane in 40 ml of tert-butanol were added at room temperature in 2 hr. After a further hour, 8% HCl was added until pH 4–5 was reached and the solution was evaporated to dryness *in vacuo*. The residue was taken up with water, the solution was neutralized with solid $NaHCO_3$ and extracted with ethyl acetate. The organic phase was thoroughly washed with water, dried over Na_2SO_4 and the solvent distilled *in vacuo*. An oily residue was obtained of (−) 2S,3S-6-[α-(2-ethoxy-phenoxy)-benzyl]-morpholin-3-one (2.6 g), $[\alpha]_D^{20} = -21.2°$.

Example 11

To a solution of 5.0 g (15.3 mmole) of (−) 2S,3S-6-[α-(2-ethoxy-phenoxy)-benzyl]-morpholin-3-one in 200 ml of anhydrous toluene, 12.7 ml (45.4 mmole) of 70% toluene solution of RED-AL (Vitride®), diluted with 40 ml of anhydrous toluene were added at room temperature in 15 min. After 4 hr the excess RED-AL was decomposed with 20 ml of 2N NaOH. The organic phase was separated, washed with water, dried, and evaporated to dryness. The residue was dissolved in ethyl acetate and 1.0 ml (15.4 mmole) of CH_3SO_3H was added to the solution. After standing overnight at room temperature, the solid (+) 2S,3S-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate was collected by filtration; g 4.9 obtained, m.p. 100–102°C; IR (KBr)cm $^{-1}$:3000–2400 (N^+H_2), 1590–1495 (arom.C=C), 1250 (Ar-O-Alk), 1205 (Alk-O-Alk), 1190, 1040 (SO_3H); $[\alpha]_D^{20} = +21.81°$.

Example 12

The (+) 2S,3S-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine (3.2 g) was dissolved in anhydrous ethanol (50 ml), then a slight excess of an ethanolic solution of hydrochloric acid was added. The solvent was evaporated to dryness under vacuo and diethyl ether was added to the oily

residue. The solid obtained after grinding was filtered to give (+) 2S,3S-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine.hydrochloride (3.3 g) m.p. 138–140°C.

By proceeding analogously, the following (+) and (−) enantiomer hydrochlorides were obtained:

(−) 2R,3R-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine.hydrochloride, m.p. 138–140°C;
(+) 2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine.hydrochloride;
(−) 2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine.hydrochloride;
(+) 2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine.hydrochloride; and
(−) 2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine.hydrochloride.

Example 13

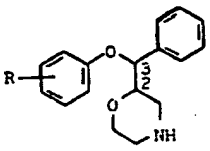
Tablets were prepared, each weighing 200 mg and each containing 5 mg of active ingredient, in the manner described below:

Composition (for 10,000 tablets)	
(+) 2S,3S-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate, the dextro (+) enantiomer deriving from the (±) RS,RS racemic form	50 g
Lactose	1.230 g
Corn starch	450 g
Talc (powdered)	50 g
Magnesium stearate	20 g.

The (+) 2S,3S-2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate, the lactose and half of the corn starch were mixed, sieved through a 0.55 mm mesh screen. 30 g of corn starch was dispersed in 300 ml of hot water. The mixture of the powders was granulated with the starch mucilage obtained. The granulate was dried and passed through a 1.4 mm mesh screen. The rest of the starch was added, as also the talc and the magnesium stearate. A careful blending was performed and the mass was compressed into tablets with 8 mm diameter punches.

CLAIMS

1. A 2R,3R or 2S,3S enantiomer of a compound of formula (I):



(I)

wherein
R is a C_1-C_6 alkoxy group or a trihalomethyl group; and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R is methoxy, ethoxy, or trifluoromethyl.
3. A compound according to claim 1 or 2, wherein the enantiomer is a dextro (+) enantiomer.
4. A compound according to claim 1 or 2, wherein the enantiomer is a levo (−) enantiomer.
5. A compound according to claim 3 selected from the group consisting of:
(+)2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine;
(+)2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine;
(+)2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine, and pharmaceutically acceptible salts thereof.
6. A compound according to claim 4 selected from the group consisting of:
(−)2-[α-(2-methoxy-phenoxy)-benzyl]-morpholine;
(−)2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine;
(−)2-[α-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine, and pharmaceutically acceptable salts thereof.
7. A compound according to any one of the preceding claims which is a hydrochloride salt.
8. A compound according to any one of claims 1 to 6 which is a methanesulphonate salt.
9. A compound according to claim 5 which is (+)2-[α-(2-ethoxy-phenoxy)-benzyl]-morpholine or a pharmaceutically acceptable salt thereof.
10. A compound according to claim 9 which is the hydrochloride salt.
11. A compound according to claim 9 which is the methanesulphonate salt.
12. A process for the preparation of a compound according to any one of the preceding

claims, which process comprises:

(a) reacting the (±)RS,RS racemic form of a compound of formula (I), as free base, with an optionally active acid so obtaining a mixture of two diastereoisomeric salts;

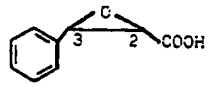
(b) separating the obtained salts by crystallization;

(c) optionally liberating the dextro (+) or levo (−) enantiomeric base from the respective separated salt; and

(d) optionally salifying the obtained dextro (+) or levo (−) enantiomeric base with a pharmaceutically acceptable salt.

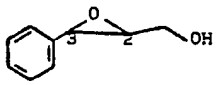
13. A process for the preparation of a compound according to any one of claims 1 to 11, which process comprises:

(a) reducing the (+) or (−) enantiomer of a glycidic acid of formula (II):



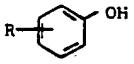
(II)

or a derivative thereof, so obtaining the (+) or (−) enantiomer of the cinnamyl alcohol-2,3-epoxide of formula (III)



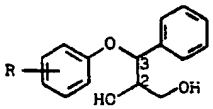
(III)

(b) reacting a (+) or (−) enantiomer of formula (III) with a phenol derivative of formula (IV)



(IV)

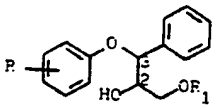
wherein R is as defined in claim 1, so obtaining a (+) or (−) enantiomer of formula (V)



(V)

wherein R is as defined above;

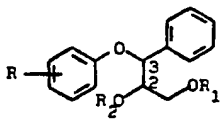
(c) esterifying a (+) or (−) enantiomer of formula (V) with a carboxylic acid, or a reactive derivative thereof, so obtaining a (+) or (−) enantiomer of formula (VI)



(VI)

wherein R is as defined above and R_1 is the residue of a carboxylic acid;

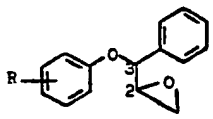
(d) esterifying a (+) or (−) enantiomer of formula (VI) with a sulphonic acid, or a reactive derivative thereof, so obtaining a (+) or (−) enantiomer of formula (VII)



(VII)

wherein R and R_1 are as defined above and R_2 is the residue of a sulphonic acid;

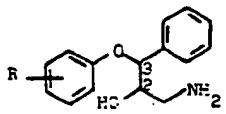
(e) making an epoxide from a (+) or (−) enantiomer of formula (VII) so obtaining a (+) or (−) enantiomer of formula (VIII)



(VIII)

wherein R is as defined above;

(f) reacting a (+) or (−) enantiomer of formula (VIII) with ammonia, so obtaining a (+) or (−) enantiomer for formula (IX)



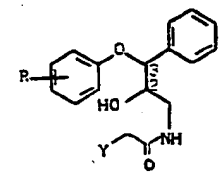
(IX)

wherein R is as defined above;

(g) reacting a (+) or (−) enantiomer of formula (IX) with a compound of formula (X)

$$Y\text{–}CH_2\text{–}CO\text{–}Y \qquad (X)$$

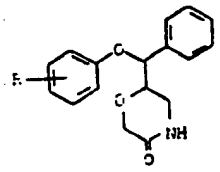
wherein Y is halogen, so obtaining a (+) or (−) enantiomer of formula (XI)



(XI)

wherein R and Y are as defined above;

(h) cyclizing a (+) or (−) enantiomer of formula (XI) so obtaining a (+) or (−) enantiomer for formula (XII):



(XII)

wherein R is as defined above; and

(i) reducing a (+) or (−) enantiomer of formula (XII) so obtaining a (+) or (−) enantiomer of formula (I) and, if desired, converting the obtained 2R,3R or 2S,3S enantiomer of formula (I) into a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound according to any one of the claims 1 to 11 as active ingredient and a pharmaceutically acceptable carrier and/or diluent.

15. A compound according to claim 1 for use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body.

16. A compound according to claim 15 for use as an anti-depressant.

17. A compound according to claim 15 for use in treating sleep disorders or as a minor tranquilizer.

18. A process for the preparation of a compound as claimed in claim 1, said process being substantially as hereinbefore described in Example 2, Examples 3 to 11 together or Examples 3 to 12 together.

19. A pharmaceutical composition substantially as hereinbefore described in Example 13.

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